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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,145	TU ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-22* is/are pending in the application.

4a) Of the above claim(s) *1-9,12-16 and 18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,11,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This is the First Office Action on the Merits of the Application filed 3 December 2003 as a continuation-in-part of application 10/053,641 filed 18 January 2002. The preliminary amendments filed 12 October 2004, 18 September 2006 and 6 April 2007 have been entered. Claims 1-22 were originally filed. Claims 8, 9, 11 and 20 were amended and claim 17 was cancelled in the 12 October preliminary amendment. Claims 10, 11, 21 and 22 were amended in the 6 April 2007 preliminary amendment. Claims 1-16 and 18-22 are pending.

Election/Restrictions

Applicant's election of Group III (claims 10, 11, 21 and 22) in the reply filed on 6 April 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-9, 12-16 and 18-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the 6 April reply.

Claim Objections

Claim 11 is objected to because of the following informalities:

The claim recites, "...producing female offspring from the male mammal that can produce hirudin encoded by the polynucleotide fragment encoding hirudin..." The phrase reads as though the male mammal produces hirudin, although it is clearly applicant's intention that the

female progeny produce hirudin. It is suggested that the claim be amended to read, "producing female offspring from the male mammal, wherein the female offspring ~~that can~~ produce hirudin encoded by the polynucleotide fragment encoding hirudin..."

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10, 11, 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The Guidelines for Written Description state "The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not

adequately described in the specification and which is not conventional in the art" (Federal Register, Vol. 66, No. 4, Column 1, page 1105).

In the instant case, the claims are directed to a method for producing hirudin using a nucleic acid construct including a polynucleotide fragment encoding hirudin. The polynucleotide fragment encoding hirudin is clearly a critical element of the claimed invention and, therefore, must be adequately described according to the requirements of 35 USC § 112, first paragraph.

The specification defines hirudin at page 6 as "any forms of hirudin or analogs thereof, naturally isolated or artificially synthesized, as long as the desired biological activity is retained." Thus, the hirudin encoding polynucleotide of the claims is generic to a polynucleotide encoding any naturally isolated or artificially synthesized analog of hirudin having the desired biological activity.

The Guidelines for Written Description state: "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus" (Federal Register, Vol. 66, No. 4, Column 3, page 1106). "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus" (MPEP §2163(3)(a)(ii)).

In the instant case, the hirudin encoding polynucleotide of the claims embraces a genus of essentially unlimited structural variants, wherein the variants exhibit some undefined "desired

biological activity". With regard to species of the invention, the application discloses the structure of a single embodiment within the scope of the claims (i.e., SEQ ID NO: 16, which encodes SEQ ID NO: 17; see especially Example 1). However, this single species clearly fails to reflect the variation within the broad genus of the claims. With regard to disclosure of relevant, identifying characteristics, the disclosure provides no guidance as to the structural features required for retaining "the desired biological activity", as stated in the specification, such that the skilled artisan would recognize a correlation between function and structure. Therefore, the one of skill in the art would not have recognized that Applicant was in possession of polynucleotides encoding "any forms of hirudin or analogs thereof, naturally isolated or artificially synthesized, as long as the desired biological activity is retained."

Although the application discloses methods by which polynucleotides encoding analogs of hirudin might be identified, an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself. It is not sufficient to define DNA solely by its principal biological property because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all DNA's that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods

first requires an adequate description of the materials, i.e. specific DNA sequences, which provide the means for practicing the invention.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of polynucleotide fragments encoding hirudin. Therefore, only the described nucleic acids comprising SEQ ID NO: 16 and encoding SEQ ID NO: 17 meet the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al. US Patent No. 4,873,316 in view of Liersch et al. US Patent No. 5,422,249 and in view of Heyneker et al. WO 91/08216, pp. 1-79.

The claims are directed to a process for producing hirudin in milk. Claim 10 comprises providing a female transgenic non-human mammal comprising a nucleic acid construct comprising in operable association a casein gene promoter, a signal sequence and a polynucleotide fragment encoding hirudin, collecting milk from the mammal and recovering hirudin from the milk.

Claim 11 comprises providing a male transgenic non-human mammal comprising a nucleic acid construct comprising in operable association a casein gene promoter, a signal sequence and a polynucleotide fragment encoding hirudin, producing female offspring from the male mammal, collecting milk from the female offspring and recovering hirudin from the milk.

Meade et al. teaches a process of producing an exogenous recombinant protein in the milk of a transgenic non-human mammal, wherein the transgenic mammal comprises a casein gene promoter and a signal peptide operably linked to a nucleic acid encoding the polypeptide to be expressed in the milk of the transgenic non-human mammal, collecting the milk and isolating the exogenous recombinant protein from the milk. (See especially, claim 1; the discussion beginning at col. 2, l. 40 and continued through col. 3, l. 29; col. 4, ll. 55-61.) In col. 7, ll. 22-30, Meade et al. teaches an embodiment wherein the female transgenic non-human mammal is provided by a method comprises providing a male transgenic non-human mammal whose genome comprises the nucleic acid construct and producing female offspring that can produce the transgene in milk.

The method of Meade et al. comprises all of the elements of the method of claims 10 and 11 except that Meade et al. does not teach that the exogenous DNA sequence coding for the recombinant protein encodes hirudin.

Liersch et al. teaches a cDNA encoding hirudin and heterologous expression of said cDNA in bacteria and yeast.

It would have been obvious to the skilled artisan to modify the teachings of Meade et al. to include the hirudin cDNA taught by Liersch for the purpose of producing hirudin from mammalian mammary glands. Motivation to combine these teachings comes from Meade et al., who teaches that the expression system disclosed therein overcomes many disadvantages of protein expression in other prokaryotic and eukaryotic expression systems (See especially col. 1, ll. 24-56). Motivation also comes from Liersch et al. who teaches that the limited availability of hirudin is a serous limitation on its use in medicine in spite of excellent biological properties. (See column 2, first full paragraph.) One would have a reasonable expectation of success in combining these teachings in light of the wide variety of proteins that have been successfully expressed in mammary glands of transgenic animals. (See, e.g., Heyneker et al. (1991; WO 91/08216) beginning on page 3, paragraph 1 through page 4, final paragraph and citations therein).

In view of the foregoing, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC § 103(a) as obvious over the art.

Claims 10 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoo et al. (2000; WO 00/15808) in view of Liersch et al. (*supra*) and further in view of Meade et al. (*supra*) and Heyneker et al. (*supra*).

The limitations of claim 10 are described above. Claim 21 is also directed to methods for producing hirudin which comprises culturing a transformed mammary gland cell comprising an expression vector comprising in operable association a casein gene promoter, a signal sequence and a polynucleotide fragment encoding hirudin under a condition suitable for expressing hirudin and recovering the hirudin.

Yoo et al. teaches an expression vector comprising a goat β-casein gene promoter (see especially "Construction of Expression Vectors" pages 5-7), for expression in mouse mammary gland derived HC11 cells (see especially beginning on page 8, last paragraph through page 10, first paragraph; and beginning on page 19, Example V). Yoo also teaches a transgenic mouse comprising the expression vector described above according to claims 13-17 of the instant application (see especially beginning on page 10, "Expression in Transgenic Mouse"; and Example VIII beginning on page 22). Yoo et al. teaches methods of producing proteins from transformed mammary gland cells in culture and recovering proteins from the culture medium for analysis (see especially Examples V and VI). Yoo et al. further teaches methods of producing proteins in transgenic non-human mammals, wherein the mice producing the milk are female (see especially Examples VII and VIII).

Yoo teaches all of the limitations of the claims except the inclusion of a signal sequence and expression of a hirudin transgene. Liersch teaches a cDNA encoding hirudin and heterologous expression of said cDNA in bacteria and yeast. It would have been obvious to the

skilled artisan to modify the teachings of Hwang to include the hirudin cDNA taught by Liersch for the purpose of producing hirudin from mammalian mammary glands or cultured cells. Motivation to combine these teachings comes from Yoo, who teaches several advantages of heterologous production of proteins in mammary glands including: high level expression leading to low production cost, easy scale up for the mass-production of target proteins; and relatively low complexity and toxicity of endogenous protein secreted from mammary gland tissue (see especially beginning on page 23, final paragraph through page 24, second full paragraph). Furthermore, Yoo et al. teaches that, "The proteins produced in mammary gland tissue-derived cells...are few in number, so that the target protein is easy to isolate and purify". Motivation also comes from Liersch who teaches that the limited availability of hirudin is a serous limitation on its use in medicine in spite of excellent biological properties (see column 2, first full paragraph). One would have a reasonable expectation of success in combining these teachings in light of the wide variety of proteins that have been successfully expressed in mammary glands of transgenic animals (e.g. see Heyneker et al (1991; WO 91/08216) beginning on page 3, paragraph 1 through page 4, final paragraph and citations therein).

With regard to the signal sequence, Meade et al. teaches the use of signal sequences from milk-specific proteins fused to polypeptides for expression in mammary gland cells and teaches that the signal sequences effect secretion and maturation of the desired recombinant protein in the mammary tissue where it is expressed. (See especially col. 3, ll. 27-30.) This teaching provides both instruction and motivation to modify the teachings of Yoo et al. and Liersch to include a signal peptide in the construct used for expression in mammary gland cells.

In view of the foregoing, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC § 103(a) as obvious over the art.

Claims 10, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson, WO 98/35689 in view of Liersch (*supra*), Yoo et al. (*supra*) and Heyneker et al. (*supra*).

The limitations of claims 10 and 21 are described above. Claim 22 is also directed to a method for producing hirudin which comprises culturing a mammary gland tissue or cell isolated from a transgenic non-human mammal comprising an expression vector comprising in operable association a casein gene promoter, a signal sequence and a polynucleotide fragment encoding hirudin under a condition suitable for expressing hirudin and recovering the hirudin.

Johnson teaches an expression vector for transforming a mammary gland cell or tissue (see especially beginning on page 27, Example 1; and beginning on page 33, Example 3), a transformed mammary gland cell containing a nucleic acid that expresses a heterologous protein (see especially beginning on page 39, Example 7), a transgenic non-human mammal comprising a DNA sequence encoding a heterologous protein and expressing said heterologous protein in a mammary gland cell or tissue (see especially beginning on page 32, Example 2; and beginning on page 34, Example 4); and a mammalian cell isolated from a transgenic non-human mammal comprising a construct comprising a DNA molecule encoding a heterologous protein operably linked to a promoter (see especially page 23, lines 35-38 and continued on page 24, line 1). On page 9, lines 26-31, Johnson also teaches that various casein promoters can be used in the vector

to express a heterologous protein in the cells and animals described above and in the first full paragraph in page 21, Johnson et al. teaches the use of signal sequences to direct secretion of the expressed polypeptide from the cell.

Johnson teaches all of the limitations of the claims except the expression of a hirudin transgene. Liersch teaches a cDNA encoding hirudin and heterologous expression of said cDNA in bacteria and yeast. It would have been obvious to the skilled artisan to modify the teachings of Hwang to include the hirudin cDNA taught by Liersch for the purpose of producing hirudin from mammalian mammary glands. Motivation to combine these teachings comes from Yoo, who teaches several advantages of heterologous production of proteins in mammary glands as described above. Also as described above, motivation comes from Liersch who teaches that the limited availability of hirudin is a serious limitation on its use in medicine in spite of excellent biological properties. One would have a reasonable expectation of success in combining these teachings in light of the wide variety of proteins that have been successfully expressed in mammary glands of transgenic animals (e.g. see Heyneker et al (1991; WO 91/08216) beginning on page 3, paragraph 1 through page 4, final paragraph and citations therein).

In view of the foregoing, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC § 103(a) as obvious over the art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel M Sullivan/
Primary Examiner
Art Unit 1636